Quantitative intranasal pollen challenges

III. The priming effect in allergic rhinitis

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The "priming effect" has been defined as an increase in reactivity of the nasal membrane following repeated exposures to pollen. Priming is reversible in days to weeks, depending on the degree of exposure to antigen. Additional characteristics of the priming effect were determined by administering ragweed pollen to only one nostril. Such challenges caused unilateral allergic rhinitis. When unilateral challenges were repeated daily they eventually caused priming or a hyperreactivity of the challenged nostril only; the resistance of the contralateral nostril was unchanged. These findings suggest that the priming effect is related to a local change in the challenged tissue rather than a systemic change. After one nostril was primed by repeated daily exposures to ragweed pollen, sorrel pollen—an antigen to which the patient had a positive skin test but which did not provoke symptoms during normal environmental exposure—was administered on the same day to both the primed and unprimed nostrils. Severe rhinitis occurred in the primed nostril during minimal exposure to this antigen; no symptoms occurred in the unprimed nostril despite a tenfold increase in the pollen dose. Evidence is presented indicating little or no cross-reactivity between ragweed and sorrel. These findings suggest that priming is non-specific.

In a previous report, I[1] described results of quantitative intranasal challenges with ragweed pollen in ragweed-sensitive patients. When pollen was administered daily, it was found that smaller doses were required on each succeeding day to cause the same or a greater degree of hay fever. The increased nasal reactivity following repeated challenges has been provisionally called "the priming effect." Environmental exposure during the ragweed-pollinating season also caused priming of the nasal membranes. Although these studies demonstrated the priming effect, they did not explain the mechanism(s) causing the effect. In the following experiments, the technique was altered in that challenges were admin-

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Read before the Section on Allergy, 116th Annual Meeting of A. M. A., Atlantic City, N. J., June, 1967.

This research was supported by Clinical Research Grant No. AI-05861 and Training Grant No. 5TI-AI-201-07 of the National Institutes of Allergy and Infectious Diseases and a grant from the Schering Corporation, Bloomfield, N. J.

Received for publication July 15, 1968.

istered to one rather than both nostrils. The change in technique provided a method for determining additional characteristics of the priming effect.

MATERIALS AND METHODS

Because of the time required, all phases of the experiment were done in only one patient. Critical portions have since been confirmed in 3 other subjects. The total experiment extended over 13 weeks and consisted of 33 hours of intranasal challenges with pollen. The date of the first challenge was April 10, 1967, and the last was performed on July 13, 1967. In the geographic area where the study was conducted, trees, grasses, and some weeds pollinate from March through July. Some of the recognized effects of this environmental pollen exposure are described in the results and discussion.

The patient in whom the following experiments were performed was a 27-year-old woman with symptoms of ragweed hay fever of 4 years' duration. Her hay fever was of moderate severity during the ragweed-pollinating season and was partially relieved by antihistamines. She was essentially free of nasal symptoms and did not use antihistamines during the remainder of the year. Nasal physical findings were within normal limits during all but the ragweed-pollinating season. The subject had never been treated with injections of ragweed extract. An intradermal skin test with aqueous ragweed extract, 100 protein nitrogen units (PNU) per milliliter, was 3 plus (15 mm. wheal). The serum, diluted 100-fold, passively sensitized the skin of a nonallergic individual to ragweed extract; greater dilutions did not transfer. A skin test was 1 plus (8 mm. wheal) to a concentration of 1,000 PNU per milliliter mixture of tree pollen extract and 1 plus (6 mm. wheal) to the same concentration of sorrel pollen extract.

A special apparatus, previously described,[2] was used to administer pollen challenges. The rate and amount of pollen administered could be controlled.

Nasal airway patency was determined[3] frequently during a challenge. Changes in patency provided one physical measure of the severity of hay fever. The nasal patency measurement is an index of functional rather than anatomical size and is given in square millimeters.

In the report cited previously,[1] the subjects inhaled through both nostrils when challenged, and total nasal patency was measured. Thus, the quantity of pollen entering each nostril and the patency of each nostril was not shown. In the experiments to be described, only one nostril was challenged with pollen, but the patency of each nostril was determined during the course of the challenge. This was accomplished by temporarily occluding one nostril with a cork during a challenge so that pollen entered the other. Nasal patency measurements were made in a similar manner: While one nostril was occluded, the contralateral nostril was measured. Preliminary experiments demonstrated that occlusion of one nostril did not affect the patency of the other. Furthermore, measurement of a nostril before and after mechanical occlusion showed that these manipulations caused no significant alteration in nasal patency.

In the present experiments, after occlusion of one nostril with a cork, the subject inhaled several times through the unobstructed nostril from the pollen

device, and the patency of each nostril after the exposure to pollen was then measured. The amount of pollen inhaled was determined. This sequence was repeated every few minutes. I discontinued challenges when a decrease in nasal patency of 50 per cent or more occurred in the challenged nostril or continued them for approximately one hour if significant nasal congestion failed to develop.

Intranasal challenges with defatted dwarf-ragweed pollen were administered to the right nostril on 29 days and to the left on 5 days during a period of 13 weeks. On 3 occasions administration of defatted sorrel pollen was given immediately after challenges with ragweed pollen to determine the effect of exposures to multiple antigens.

Since the objective of this work was to produce a laboratory challenge with ragweed pollen which could be compared with environmental pollen exposure, I first determined what constituted environmental exposure. To do this, I did pollen counts on 2 or 3 occasions daily in the New York City suburbs during the ragweed-pollinating seasons of 1966 and 1967. Counts were made with a modified Hirsch spore trap having a calculated efficiency of 90 per cent. The great majority of counts in each year were below 0.3 grain per liter. The highest count in 1966 was 0.67 grain per liter and, in 1967, 0.7 grain per liter. Assuming a resting tidal volume of 8 liters per minute and that 100 per cent of the pollen in the air enters the nose during inspiration, approximately 6 pollen grains would enter the nasal passages every minute on the days when the highest counts were recorded. This theoretical rate of environmental challenge will obviously be maintained only under the conditions outlined. Changes in tidal volume, surroundings, etc., will alter the rate markedly. Nonetheless, the figure of 6 grains per minute provides one standard for environmental exposure which may be compared to results of laboratory exposures. Since the laboratory challenges were administered to only one nostril, I have assumed a pollen inhalation rate of 3 pollen grains per minute for one nostril is equivalent to environmental exposure on the days when highest counts were recorded. This rate is defined as a "severe hay fever day" for purposes of discussion only.

Since my previous report,[2] improvements have been made in the scanning device of the pollen-dispensing apparatus so that the scanner now traps one out of every 2 grains passing through the tube to the patient. This figure was determined experimentally by substituting a modified Hirsch spore trap at the point in the tube normally occupied during a challenge by the patient's nose and by using airflow rates similar to those produced by most patients when inhaling from the mask (30 L. per minute).

In laboratory challenges the pollen is delivered to within ¼ inch of the patient's nares by inspiratory effort. Since there is no deflection of airflow in the ¼ inch between the end of the pollen delivery tube and the nares, I assume that the pollen enters the nose, although this cannot be confirmed with existing techniques.

Challenges were performed in an air-conditioned room. The relative humidity varied between 40 and 50 per cent and the temperature between 68 and 80 degrees Fahrenheit. Variation in temperature and humidity within the range specified had no obvious effect on the results.

The subject noted that after several successive days of challenge, hay fever symptoms which subsided after challenge sometimes recurred later in the day. These symptoms were precipitated by going out of doors onto the street and into the subway. In my previous report,[1] I described recurrence of symptoms some hours after challenges were completed and attributed their occurrence to exposure to other antigens or nonallergic stimuli. These extraneous antigens or nonallergic stimuli never caused symptoms normally but could have done so if the nasal membranes were primed. On rare occasions during the 13 weeks of the experiment, the subject took an antihistamine tablet to control these symptoms. Antihistamines were never taken in the 12 hours preceding a day's challenge.

RESULTS

Priming of the right nostril

Challenge of the right nostril one hour daily for 5 consecutive days in the first week "primed" the right nostril: With each succeeding day, a smaller dose of pollen produced marked hay fever symptoms and a significant decrease in nasal patency (Fig. 1 and Table I). Challenges performed during the next 3 weeks produced similar results (Table I). In addition, with each succeeding week of challenge the right nostril became progressively more reactive as compared with the preceding week. The extent of the priming effect is shown in Fig. 2.

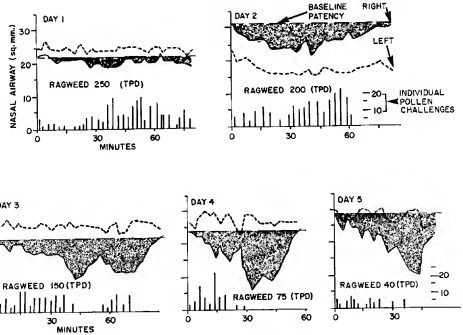

Fig. 1

Challenge of right nostril on 5 consecutive days. Unless otherwise specified, the following key identifies the data in the illustrations: patency of the right nostril (———); patency of the left nostril (- - - -); base-line patency of challenged nostril (———); dotted area is the decrease in patency of the challenged nostril. TPD = total pollen dose in pollen grains of ragweed. Vertical lines indicate individual pollen challenges.

On the first day of challenge, 250 ragweed pollen grains caused insignificant nasal congestion, whereas by the fifth day of the third week, 7 grains produced marked congestion.

Reversible nature of the priming effect

Challenges were omitted for a number of days after priming. To produce equivalent nasal congestion then required administration of a larger pollen dose than that given the last time the patient was challenged (Table I). Fig. 3 illustrates this finding on 3 different occasions. Omission of challenge between Days 5 and 8 caused complete reversal of the priming effect: 40 pollen grains on Day 5 caused nasal congestion, but on Day 8, 250 pollen grains produced insignificant congestion. Reversal of the priming effect also occurred during the weekend following the third week of challenge (Days 19 to 22). However, recovery was incomplete, as 135 pollen grains administered on Day 22, 3 days after the last pollen exposure, caused significant nasal congestion compared with earlier challenges when 250 grains administered 3 days after the last exposure did not produce congestion. Elimination of challenge between Days 26 and 37 and in the ninth week, after 3 weeks without challenge, also illustrates only partial recovery. The patient was not challenged again until the thirteenth week. At this time, 302 pollen grains administered to the right nostril caused neither symptoms nor a decrease in nasal patency, indicating that complete recovery occurred when challenges were eliminated for 4 weeks.

The time required for reversal of the priming effect appears to be related to: (1) the number of successive days of challenge; and (2) the number of days between challenges.

Table I. *Quantitative nasal pollen challenges (unilateral)*

Week	*Days*	*Sunday*	*Monday*	*Tuesday*	*Wednesday*	*Thursday*	*Friday*	*Saturday*
1	1-6		>250*	>200	150	74	40 (>180)†	–
2	7-13	–	250	150	140	125	30 (>302)	–
3	14-20	–	150	140	50	46	7	–
4	21-27	–	135	65 14S‡	49 (>140S)	29 10S	7	–
5	28-34	–	–	–	–	–	–	–
6	35-41	–	–	94	44	35	25	–
7	42-48	–	(>200)	(>150)	Spontaneous hay fever			
8		–	–	–	–	–	–	–
9		–	>118	–	–	–	>169	–
13			>302					–

Challenge was to right nostril unless indicated.

Challenge was with defatted ragweed pollen unless indicated.

*Number of pollen grains which caused a 50 per cent decrease in nasal patency.

†Parentheses indicate challenge of left nostril.

‡S = challenge with defatted sorrel pollen.

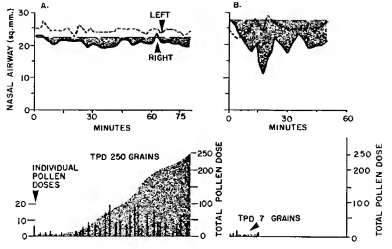

Fig. 2

Increase in reactivity of right nostril following repeated daily challenge: first challenge, *A*, compared with fifteenth challenge, *B*. Upper panels illustrate changes in nasal patency; lower panels show individual pollen challenges (vertical bars) and cumulative pollen dose (stippled area).

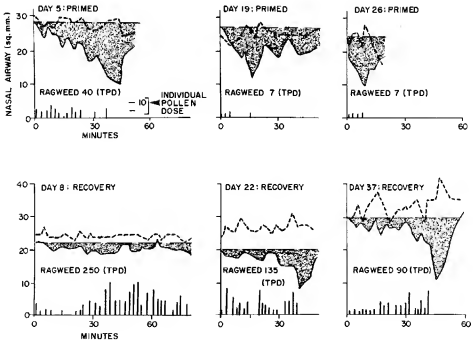

Fig. 3

Reversibility of the priming effect. Primed days (5, 19, 26) show challenges on the last day of a series of daily challenges. Recovery days (8, 22, 37) are the first challenges done after a number of days without challenge. See text for full description.

Local nature of the priming effect

The patency of the left nostril did not change during administration of pollen to the right nostril even though severe hay fever and nasal congestion occurred on the right (Fig. 1), indicating that the acute allergic reaction is limited to the challenged tissue.

Although acute hay fever occurred only in the challenged nostril, it was possible that challenges repeated daily which caused priming of the exposed nostril might also cause priming of the unchallenged side. To determine whether priming the right nostril affected the left nostril, the left nostril was challenged occasionally during the 13 weeks of the experiments. Fig. 4 illustrates such a challenge on Friday of the second week. The right nostril, primed by repeated challenges during the first 2 weeks, became severely congested during administration of 30 pollen grains in the morning. In the afternoon, patency of the left nostril did not change during challenge with 302 pollen grains, and hay fever symptoms did not develop.

I repeated the preceding experiment in the seventh week, since the possibility existed that frequent challenges of the right nostril over a period of weeks might affect the reactivity of the left nostril. However, challenge of the left nostril on Monday and Tuesday of the seventh week did not cause congestion or symptoms of hay fever.

During the seventh week, I planned to continue challenging the left nostril. This was not possible, for on Wednesday of this week severe spontaneous hay fever occurred and continued for several days. This attack took place during the tree-pollinating season at a time when patients sensitive to tree pollen experienced severe hay fever symptoms. The subject was minimally sensitive to trees by skin test but had never experienced clinical symptoms during the tree-

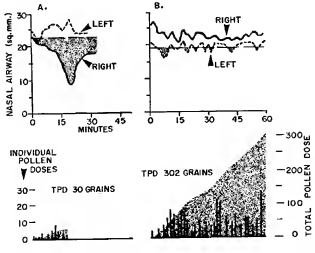

Fig. 4

Challenge of the right nostril, *A*, and left nostril *B*, on the same day. The right nostril had been challenged on 9 of the 11 preceding days and was therefore primed. The left nostril had been challenged only once in the preceding 11 days and was not primed.

pollinating season before. It is possible that tree pollen in the environment caused the subject's spontaneous hay fever symptoms at that time but that symptoms occurred only because of nasal priming produced by the prior ragweed challenges.

Nonspecificity of priming

The experiments described show that recent exposures to ragweed pollen increased the patient's reaction to subsequent ragweed challenges, but they do not provide information concerning specificity of priming. To determine the specificity of the increase in reactivity, the subject's right nostril, which had been primed with ragweed, was then challenged with sorrel pollen. Challenge of the left unprimed nostril with sorrel served as a control. The subject had a weakly positive skin test to sorrel but had never had clinical symptoms during the sorrel-pollinating season. Table I, fourth week, and Fig. 5 illustrate the results. On Tuesday of the fourth week, 65 ragweed pollen grains rapidly caused an acute episode of allergic rhinitis in the primed right nostril. At the height of the attack, pollen exposure was stopped and administration of carbon particles ranging in size from less than 1 μ to greater than 40 μ (the average diameter of ragweed pollen is 20 μ) was begun. The carbon particles served as a control to determine whether inert nonallergenic substances would cause an increase in symptoms. During administration of carbon particles, all hay fever symptoms subsided and nasal patency increased, suggesting that size and quantity of inert particles did not cause or sustain hay fever symptoms. Minimal exposure of the

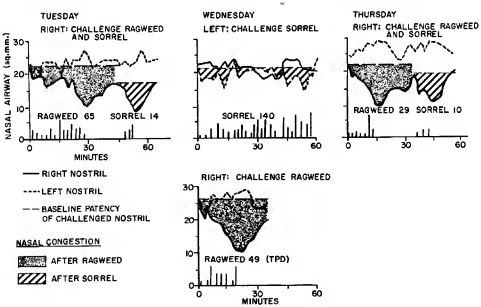

Fig. 5

Effect of exposure of the right nostril to sorrel pollen (Tuesday and Thursday) after the right had been primed with ragweed. Effect of sorrel challenge alone on the left nostril (Wednesday). The left had not been previously challenged and therefore was not primed.

right nostril to sorrel pollen began after carbon particle exposure ceased and caused immediate exacerbation of symptoms and decrease in nasal patency. No symptoms or changes occurred in the left nostril.

On the following day, symptoms again developed rapidly in the primed right nostril during challenge with ragweed. Later in the day, neither symptoms nor nasal congestion occurred in the left nostril (not primed with ragweed) after challenge with 140 sorrel pollen grains. This dose was 10 times the number of grains which caused marked symptoms in the right nostril on the preceding day.

On Thursday, the experiment performed on Tuesday was repeated. Again, nasal congestion developed rapidly during ragweed administration, patency increased when ragweed was stopped, and congestion rapidly returned when sorrel was begun.

DISCUSSION

In a previous report[1] I showed that if the nasal membranes of ragweed-sensitive patients are challenged daily with pollen, the membranes become more reactive, or "primed," on each succeeding day of challenge. These experiments did not clarify the mechanism underlying priming.

In the present study, the technique was modified to the extent that pollen was administered unilaterally. Unilateral challenges of pollen caused acute episodes of allergic rhinitis only in the nostril challenged. By the use of unilateral pollen challenges, systemic and local effects of challenge could be separated.

Daily unilateral pollen challenges primed only the nostril challenged. Eventually, this nostril reacted markedly to less than one fortieth of the pollen dose which had originally produced no difficulty. The priming effect was shown to be reversible. After one hour of challenge daily for 5 consecutive days, elimination of challenge for 2 days completely reversed the priming effect. After challenges had been given on weekdays for 4 weeks, 10 days without challenge only partially reversed the priming effect. When 4 additional weeks elapsed (ninth to thirteenth weeks) without challenge, the priming effect was completely reversed. These findings indicate that the time required for reversal of the priming effect is related to the duration of the challenges and the interval between them.

The priming effect clarifies a number of clinical observations about hay fever for which there have been no logical explanations. We have shown that prior to the ragweed-pollinating season the nasal membrane is not primed, and in the unprimed condition it is relatively resistant to antigenic challenges.[1] At this time a large pollen dose would be required to produce even mild symptoms and nasal congestion. Consequently, early in the ragweed-pollinating season, even though pollen is in the environment, patients generally report few symptoms. However, in time the continuous environmental exposure, even though mild, gradually primes the nasal membranes. Thereafter, as environmental pollen concentration increases, symptoms appear and become more severe. The increase in symptomatology could be related to: (1) the fact that nasal membranes are now primed; (2) the increase in pollen concentration; or (3) a combination of both factors. Experimental results suggest that both factors are significant but

that the priming effect is the more important. The priming effect is of much greater clinical significance later in the season. At this time, symptoms continue unabated or may even increase in severity in a significant number of patients despite the fact that pollen exposure is minimal or absent. Persistence of symptoms probably occurs for 2 reasons. First, the nasal membrane is primed and will react to minute amounts of ragweed pollen. Second, because the patient is primed by the seasonal exposure, symptoms will also occur following exposure to other antigens to which the patient is minimally sensitive and which normally cause no reaction.

Nonspecificity of priming was demonstrated by priming with one pollen followed by challenge with a different pollen. The subject described had a moderately positive ragweed skin test but only a minimally positive sorrel skin test. She had ragweed hay fever symptoms during the ragweed-pollination season but never experienced hay fever symptoms during sorrel pollination. Neither symptoms nor nasal congestion occurred during provocative challenges with sorrel, when the nasal membrane was not primed. However, after this subject was primed with ragweed, a minute sorrel challenge produced severe allergic rhinitis. Challenge with carbon particles of the same size as sorrel administered under similar conditions produced no symptoms, showing that sorrel acted as an allergen and not as a nonspecific irritant.

The concept that priming is nonspecific is extremely fundamental to the science of allergy, and, therefore, a crucial objection to the findings must be considered. Ragweed and sorrel pollen are 2 distinct botanical entities. Nevertheless, they are complex particles and at this time have not been completely analyzed chemically or immunologically. Therefore, a degree of cross-reactivity between them may exist. If they do cross-react to a significant degree, the claim for immunological nonspecificity of priming may be inaccurate. Since the disease studied, allergic rhinitis, is mediated by skin-sensitizing antibody (SSA), cross-reactivity, or it's absence, should be demonstrated by techniques with the use of SSA. One test for specificity of SSA is neutralization in passive transfer experiments. In the case presented, this method could not be used to its full extent because sorrel antibodies were present in such low titer that they did not transfer. However, I was able to show that sorrel extract did not neutralize skin-sensitizing antiragweed antibodies in this subject's serum but that an equivalent amount of ragweed extract neutralized 90 per cent of antiragweed SSA. Cooke[4] showed, by using the neutralization of SSA technique, that little or no cross-reactivity existed between aqueous extracts of sorrel and low ragweed, although he demonstrated this on only one serum.

Another procedure for determining specificity is to compare skin-test reactions to different antigens in the same individuals. If cross-reacting antigens are present in concentrations greater than 1 per cent, those patients with 3 plus and 4 plus skin reactions to ragweed should all have, respectively, 1 plus and 2 plus skin tests to sorrel extract of the same concentration. This was not the case. Of 25 patients with 3 plus or 4 plus ragweed skin tests, 17 had negative sorrel tests, indicating less than one per cent cross-reactivity. Even if ragweed and sorrel had common antigenic determinants of the order of 10 per cent, it would

be highly unlikely that this amount of cross-reactivity would be sufficient to cause allergic rhinitis in the experiment described. In summary, the available evidence suggests that no appreciable cross-reactivity exists between sorrel and ragweed, and, therefore, the concept that priming is nonspecific is valid.

The finding that priming with one antigen increases the reactivity of a patient to a second antigen for which he may have only a mild sensitivity, and quite possibly to all antigens to which a sensitivity exists, indicates that the etiology of a specific episode of allergic rhinitis may be more complex than previously suspected. Thus, a pollen to which the patient is clinically sensitive may be ineffective in producing symptoms for a given dose at one time, yet on another occasion the same or even a smaller dose may cause severe symptoms. Furthermore, an antigen to which a patient has minimal sensitivity and one which usually does not cause symptoms may under special circumstances, in very minute doses, precipitate severe hay fever. Or, simultaneous exposure to 2 or more inhalant antigens may cause clinical symptoms when exposure to only one would produce no difficulty.

Whether a positive skin test with an allergen indicates allergy has often been questioned. Holt,[8] in a recent report, suggests that the skin test should be considered as a false positive reaction, and the subject should not be considered allergic to an antigen when the antigen causes a positive skin test but environmental exposure does not produce allergic symptoms. Applying these criteria to my patient, the mildly positive skin test to sorrel would have to be considered a false positive reaction since she did not have symptoms during environmental exposure. That the sorrel skin test indicates true immunologic sensitivity was demonstrated when an allergic attack resulted during sorrel challenge under appropriate circumstances.

Unilateral pollen challenge showed that the priming effect was related to a local change and not to systemic alterations. Even after the right nostril was primed by weeks of challenge and reacted to small doses of pollen, the left nostril was still found to be resistant to challenge with much larger pollen doses.

Unfortunately, in an experiment extending over 13 weeks it was impossible to control the patient's environment during periods when she was not being challenged. This undoubtably resulted in many exposures to multiple antigens in the environment during the course of the experiment. I suspect that some of these antigens may have caused acute episodes of allergic rhinitis. For instance, the patient developed acute rhinitis for several days, as previously mentioned, during the tree-pollinating season. Fortunately, this episode occurred during the seventh week, when the major portion of the experiment had been completed. On some occasions, after days of challenge in the laboratory, the patient had symptoms of hay fever recur when she left the hospital to go home. I feel that these symptoms developed only because the nasal membrane had been previously primed with ragweed and that priming made her more reactive to environmental antigens, such as dust, for which she had only minimal skin-test sensitivity and, ordinarily, no clinical reactivity. Although the extraneous exposures to antigens caused occasional mild episodes of allergic rhinitis, it is highly unlikely that the major findings of the study were affected by them.

We do not know why antigen exposure increases nasal reactivity. Nevertheless, the characteristics elucidated in this study, that priming is a *local* change, that it is *nonspecific*, that it can begin in a few days, and that it is reversible in a few days, eliminate some hypothetical mechanisms while strengthening the arguments for others. Systemic changes in skin-sensitizing antibody titer[6] or alterations in the histamine-releasing capacity of leukocytes[7] can be eliminated as mechanisms responsible for priming, since priming is local and in the early stages is reversed by as little as 48 hours without challenge. An increased synthesis of skin-sensitizing antibodies locally in the challenged tissue is one possible explanation for priming. To support this contention one must assume that some antibody-forming cells reside in the nasal membranes or that the stimulus of the pollen challenge attracts them to the local nasal tissues. Since priming must be provisionally considered nonspecific, the second part of this hypothesis requires that the chemotactic stimulus be nonspecific; i.e., ragweed pollen challenges must attract not only ragweed skin-sensitizing antibody forming cells but also cells with other antigen specificities. This hypothesis cannot be verified or discredited by the data presented. Another likely explanation of the mechanism causing priming is associated with local tissue changes. Substances absorbed from pollen landing on the nasal mucosa could release, or could be, chemotactic agents which attract antibody-containing cells or cells containing chemical mediators to the nasal tissues challenged. If subsequent antigen exposure occurred while these cells were in the nasal tissues, allergic rhinitis could follow more rapidly than during previous exposures. One nonimmunological explanation is that the antigen, antigen-antibody complexes, or events in allergic inflammation may alter the local tissues physically or chemically so that a subsequent exposure is more efficient in producing an allergic reaction.[6]

The priming effect appears to be a hyperreactivity of the nasal tissues caused by repeated allergenic stimulation. Priming occurs because of local rather than systemic changes. These experiments suggest that priming is nonspecific since a patient primed by one antigen is also primed to other antigens even when sensitivity is minimal. The tissue mechanisms responsible for the priming effect are not known.

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